EXHIBIT K

Int Urogynecol J (2008) 19:467–471
DOI 10.1007/s00192-007-0465-y

ORIGINAL ARTICLE

A randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocoele

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Received: 10 June 2007 / Accepted: 3 September 2007 / Published online: 28 September 2007

Abstract The aim of this study was to compare the efficiency of polypropylene mesh surgery with the site-specific repair surgeries in the treatment of cystocoeles. We randomized 90 patients into two groups according to a computer-based program. After a 12-month (mean) follow up, we noticed that the polypropylene mesh surgery yielded good anatomical results. Acceptable anatomical cure rates were 91 and 72% in the mesh surgery group and site-specific surgery group, respectively. There were three cases (6.9%) of mesh erosion. One case of urinary retention and two cases of de novo dyspareunia were seen in the mesh surgery group. De novo stress urinary incontinence developed in three patients in the site-specific surgery group. We concluded that surgery with light polypropylene mesh (Sofradim®, Parietene) is superior to the site-specific surgery in the treatment of cystocoeles.

Keywords Polypropylene mesh surgery · Site-specific repair · Cystocoele

Introduction

Pelvic organ prolapse (POP) is not a life-threatening pathology, whereas it is a condition which lowers the quality of life [1]. It is well-known that POP is caused by loss of supporting connective tissue and muscle structures of pelvic organs. The restoration of the supporting mechanisms is a prerequisite to treat the condition. However, despite modifications and evolutions in site-specific POP surgery, there is still an unacceptably high recurrence rate that could be as high as 70% in the anterior compartment of the vagina [2]. As a matter of fact, due to high recurrence rates, surgeons have been in search of new surgical techniques, and Parker opened a gate in urogynecology by placing a synthetic mesh (Marlex) to the vagina for the first time in 1993 [3].

In this study, we aimed to compare the efficiency and complications of polypropylene mesh surgery with the site-specific surgery in the treatment of cystocoele.

Materials and methods

The study has been carried out in the urogynecology clinics of Ankara Etlik Maternity and Women's Health Teaching Hospital between January 2006 and January 2007.

Ninety (90) patients diagnosed as having cystocoele were randomized according to a computer-based program either to polypropylene mesh surgery or site-specific cystocoele repair (Fig. 1). Patients who had stress urinary incontinence or concomitant rectocoele or enterocoele or recurrent cystocoele were excluded from the study. Forty-five (45) patients were operated with the polypropylene mesh surgery, and two patients were lost to follow-up. All patients were operated by the vaginal route using low weight (light) mesh (Sofradim®, Parietene). Forty-five patients were operated with site-specific cystocoele repair (40, 3, and 2 patients underwent colporrhaphy anterior, paravaginal defect repair, colporrhaphy anterior + paravaginal defect repair, respectively), and three patients were lost to follow-up. The study did not include the lost cases.

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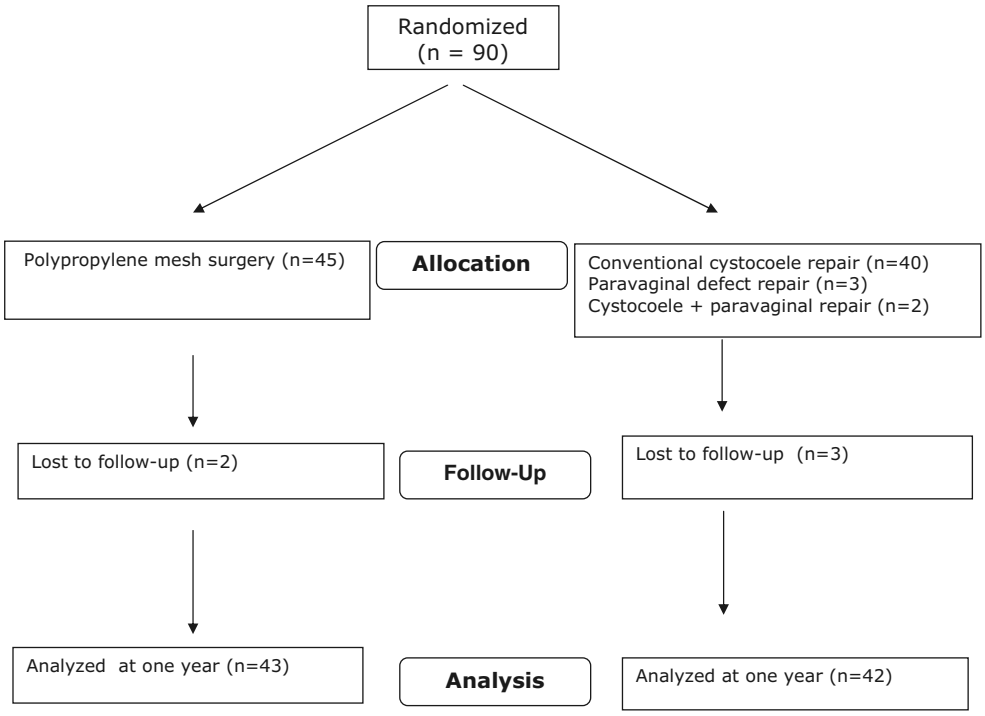
Fig. 1 Randomization chart



Preoperative and postoperative evaluation included a complete clinical history, urogynecologic examination (stress test, *Q*-tip test, stress cough pad test), neurological examination (clitoral reflex, anal reflex, and cough reflex), urinalysis and urine culture, fasting blood glucose and calcium testing, urodynamic studies, and pelvic ultrasonography.

The patients were evaluated with pelvic organ prolapse quantification (POP-Q) staging system on maximum Valsalva effort in the lithotomy position. The acceptable surgical cure was defined when the leading edge of cystocoele was <−1 cm in relation to hymen (stage 1). The women also completed a prolapse quality of life questionnaire (P-QOL) [5], validated for the Turkish women pre- and postoperatively.

All proven urinary tract infections were treated with appropriate antibiotics before surgical intervention. Moreover, the patients who were at the menopausal period were given vaginal estrogen treatment 2 weeks before surgery. Besides, all patients were given antibiotic treatment for 3 days after the surgery. The patients were instructed to rest for 2 weeks postoperatively. They were allowed to return to work after 4 weeks, to have sexual intercourse after 12 weeks. Patients were followed up at 6 weeks, 6 months, and annually after the operation with further clinical history, examination, and where appropriate, urodynamic study. All of the patients gave an informed consent before the surgical procedures, and the ethics committee of the hospital accepted the study. All operations were performed by the first author (AAS). All patients were reviewed postoperatively by another surgeon who did not participate in the operations. All of the patients were asked how they felt just the day after surgery.

The reported pelvic organ prolapse cure rates for the standard cystocoele repair and polypropylene mesh surgery for cystocoele were 30 and 89%, respectively [2, 4]. To have 80% power to detect this difference and to limit the chance of type I error to 5%, the number of patients for each group was estimated to be 40. We decided to add approximately 10% to this concerning loss to follow up. Therefore, the total sample size was calculated to be 90 patients (45 in each arm) (α=0.1). All the data was recorded using standard forms. The comparisons in groups and intergroups (between group I and group II) were made by Wilcoxon test and chi-square test, respectively. The study was not funded by an organization and the authors have no commercial interests with the products used in the study. The surgical interventions were performed as follows.

Table 1 Demographic characteristics of each group

Demographic data	Group I (mean±SD)	Group II (mean±SD)	*p* value
Age (years)	57.7±9.4	50.1±9.9	>0.05
Body mass index	29.4±4.1	30.3±5,6	>0.05
Parity	3.1±1.4	3.7±1.9	>0.05

Table 2 Preoperative and postoperative POP-Q of cases in both groups

Cases	Group I (mesh surgery)			Group II (site specific surgery)		
POP Q point	Pre-op (mean)	Post-op (mean)	*P* value	Pre-op (mean)	Post-op (mean)	*P* value
Aa	0.5	−2.3	0.003	0.3	1	0.743
Ba	2.7	−2.4	0.001	2.8	0	0.008
C	−2	−6.7	0.006	−2.7	−2.9	0.745
Gh	4.5	3	0.042	4	3.4	0.048
Pb	2	2	0.980	1.5	1.5	0.790
Tvl	8	8	0.970	7	7	0.854
Ap	−2.6	−3	0.694	−2.7	−2.7	0.756
Bp	−2	−2	0.876	−2	−2	0.957
D	−8	−8	0.853	−7	−7	0.872

The polypropylene mesh surgery

A nonabsorbable, macroporous monofilament polypropylene light mesh (Sofradim®, Parieten) was used as the synthetic material. A trapezoid four-armed mesh was cut from a polypropylene 30×30 cm mesh sheet. The upper border, the lower border, and the height of the cut mesh were 4, 8, and 6 cm, respectively. A full thickness vertical incision extending 1 cm below the urethral meatus to 2 cm above the anterior lip of cervix was made. The Halban fascia was left over the flaps of anterior vaginal wall. The synthetic mesh was placed under the bladder and secured bilaterally by two arms through each obturator foramen. There were two entrance points in each obturator foramen. The first point was in the genitofemoral folds at the level of the clitoris, the second point was 2 cm lateral and 3 cm inferior to the superior point. These points were cut 0.5 cm long with a knife. For the upper point entrance, the tip of the needle contacted to the skin at 90° and perforated the adductor longus muscle and obturator foramen where the tip of the needle met with the index finger. The handle of the needle was turned approximately 90° medially, and the needle circulating behind the medial edge of the ischio-pubic ramus was taken out from the incised vagina under the guidance of index finger. The upper arm of the mesh was carried to the perineal skin by exteriorizing the needle. For the lower point entrance, the tip of the needle perforated the lower incision with the handle parallel to the ischio-pubic ramus. The tip of the needle was advanced under the levator plate up to 0.5 cm caudal to the ischial spine. Then, the handle of the needle was turned 45° medially, and the needle exited from the vaginal incision perforating the iliococcygeus muscle. The lower arm of the synthetic mesh was carried out to the perineal skin by exteriorizing the needle. The same procedure was carried out contralaterally. Therefore, the four arms of the mesh were exteriorized to the perineal skin. Afterwards, the mesh was positioned in a tension-free manner under the bladder. The lower part of the mesh was fixed to the cervix with a polyglactin 910 synthetic absorbable suture (Vicryl®) after cutting excess part of the synthetic mesh. The vaginal incision was sutured with polyglactin 910 continuously.

The site-specific cystocoele repair

A vertical incision extending 1 cm below the urethral meatus to 2 cm above the anterior lip of the cervix was made [6]. The pubocervical fascia was identified and separated from the vaginal mucosa with sharp and blunt dissection. The defective part of the pubocervicovaginal fascia was sutured with absorbable polyglactin 910 (Vicryl) suture material. We choose polyglactin 910 as a suture material because it permits easy tissue passage, precise knot placement and smooth tie-down, absorption is minimal for 40 days and is completed in 56–70 days. The excess vaginal mucosa was not trimmed off and the vaginal incision was closed with continuous sutures. Moreover,

Table 3 Comparison of postoperative POP-Q points between group I and group II

Points	Aa2	Ba2	C2	Gh2	Pb2	TVL2	Ap2	Bp2	D2
Aa1	0.004*								
Ba1		0.003*							
C1			0.004*						
Gh1				0.290*					
Pb1					0.060*				
TVL1						0.920*			
Ap1							0.084*		
Bp1								0.075*	
D1									0.073*

1 Stands for group I, *2* stands for group II
*Pearson chi-square value (*p* value)

when paravaginal defect exists, the pubocervical fascia was fixed to the arcus tendineous fascia pelvis (ATFP) with necessary number of (approximately two to three) stitches of absorbable polyglactin 910 sutures vaginally.

Results

The study population was 90 patients. Forty-five (45) patients randomized to the polypropylene mesh surgery and formed group I, and 45 patients randomized to site-specific cystocoele repair and formed group II.

The mean time at follow up was 12 months (minimum 8–maximum 16 months) of both groups. The overall efficacy rates, in terms of anatomical reconstruction, were 91% (39/43) and 72% (30/42) in groups I and II, respectively, which was statistically significant ($p<0.05$). There was no difference between groups in terms of age, body mass index, and parity. The details are given in Table 1. Table 2 shows preoperative and postoperative POPQ staging system values. A remarkable recovery was seen in polypropylene mesh surgery group.

Table 3 shows the comparison of postoperative POP-Q points between groups I and II. A statistically significant difference in the localization of postoperative points of Aa, Ba, and C points between groups were observed ($p<0.05$); however, no statistically significant difference was observed for the points of Gh, Pb, TVL, Ap, Bp, D between groups ($p>0.05$). The postoperative localization of points Aa, Ba, and C moved upwards in group I, which were statistically significant when compared with group II ($p<0.05$). The genital hiatus (gh) also constricted in both groups that would be able to prevent cystocoele prolapse; however, the postoperative length change was not statistically significant between groups, although the change was statistically significant for each group ($p>0.05$). The change in the localization of the postoperative Pb, TVL, Ap, Bp, and D points were not statistically significant between two groups. In the same way, no statistically significant difference was observed in each group ($p>0.05$), and besides, we named POP-Q stage 0 and 1 as cure, stage 2 to 4 as failure. The difference was statistically significant between two groups (Pearson Chi-square value 0.0044, $p<0.05$, Table 4).

Table 4 Comparison of groups in terms of anatomical outcomes

Parameters	Group I	Group II	*P* value
Number of 'cure'	39	30	0.0044
Number of 'failure'	4	12	0.0044
Number of patients	43	42	

Table 5 Preoperative and postoperative P-QOL scores in both groups

Parameter	Group I (mesh surgery)			Group II (site specific surgery)		
	Pre-op	Post-op	*P* value	Pre-op	Post-op	*P* value
PQOL score (mean±SD)	29.5±26.1	6.2±5.5	<0.05	32.4±28.5	7.5±6.2	<0.05

Preoperative and postoperative prolapse quality of life (P-QOL) questionnaires were completed by each patient. A remarkable improvement in the scores of QOL in both groups has been observed. The changes in the scores of preoperative and postoperative assessment were statistically significant in each group (Table 5). Besides, urinary symptoms such as abnormal emptying, frequency, urgency, and pelvic pain improved statistically in the mesh surgery group. However, only abnormal emptying and urgency statistically improved in the site-specific surgery group (Table 6). There were three cases (6.9%) of mesh erosion (3/43). The visible graft was excised and the vaginal mucosa sutured under local anesthesia. No recurrence was observed after 1 month follow up.

Urinary retention was seen in one patient postoperatively in group I . After inserting Foley catheter to the bladder and leaving it for 3 days, she did well. De novo dyspareunia was observed in two patients (4.6%) in the mesh surgery group. No dyspareunia was seen in the site-specific surgery group. De novo stress urinary incontinence developed in three patients (7%) in the site-specific surgery group. No patients developed stress urinary incontinence in the mesh surgery group. No mesh shrinkage was noticed in the mesh surgery group during the follow up period.

Another important point that should be stressed is that our observation on patients just the day after the mesh surgery. All of the patients were very comfortable, happy and had a feeling

Table 6 Preoperative and postoperative urinary symptoms in both groups

Urinary symptoms	Group I (mesh surgery)			Group II (site specific surgery)		
	Pre-op (n)	Post-op (n)	P value	Pre-op (n)	Post-op (n)	P value
Abnormal emptying	5	0	<0.05	7	2	<0.05
Frequency	14	3	<0.05	7	3	>0.05
Urgency	8	1	<0.05	13	1	<0.05
Nocturia	4	2	>0.05	2	1	>0.05
Pelvic pain	16	1	<0.05	8	4	>0.05

of 'healthy state'. We named this condition as 'pelvic well-being'. Whereas, the above clinical observation was only noticed in five patients in the group of site-specific surgery.

Discussion

Yan et al. reported the efficiency and feasibility of polypropylene mesh usage in the treatment of cystocoele repair [7]. Besides, the erosion rate was given as 7%, which was similar to our result. Moreover, in our study, we observed that the postoperative points of Aa, Ba, and C were significantly moved upwards, and the difference was remarkably in favor of polypropylene mesh surgery when compared with site-specific surgery ($p<0.05$). There were no statistically significant difference in the postoperative localization of points Gh, Pb, TVL, Ap, Bp, D between groups ($p>0.05$). As no intervention was performed at the posterior compartment of vaginal wall, the results should be expected in this manner. Moreover, the comparison of data of the anterior vaginal compartment showed that polypropylene mesh surgery was advantageous over site-specific surgery for the treatment of cystocoele ($p<0.05$) from the point of anatomical outcomes ('cure' or 'failure').

In their literature review, Maher et al. documented the high success rates of mesh surgery over standard anterior colporrhaphy, 75–100 and 37–57%, respectively [8]. In our study, the success rates of polyproylene mesh surgery and cystocoele repair were 91 and 72%, respectively. The difference was statistically significant ($p<0.05$). On the other hand, a randomized study comparing polyglactin 910 mesh with standard anterior colporrhaphy pointed out that mesh surgery was not superior over traditional ones [2]. A study, using low-weight polypropylene mesh, showed very low recurrence rates for cystocoele repair which was 6.8% [4]. Our recurrence rate was 9%. Sand et al. randomly allocated patients for anterior colporrhaphy alone or anterior colporrhaphy plus polyglactin mesh surgery. The success rate in the mesh group was %75, which was significantly greater than anterior colporrhaphy alone [9].

In their retrospective study, Dwyer et al. [10] reported that synthetic polypropylene mesh placement to the vagina was with good anatomical and functional outcomes. However, the authors also added that long-term results should be waited. We should also mention that a midline plication with a permanent suture or polydioxanone (PDS II) remains to be compared with polypropylene mesh. Although the study population is relatively small and the follow up period is short, we claim that polypropylene mesh surgery yields good anatomical and functional results for the treatment of cystocoeles in primary cases.

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